REMARKS

The Office Action dated April 3, 2003 has been received and carefully studied.

By the accompanying amendment, the specification has been amended to reference the PCT application and to include an abstract as a separate sheet.

The Examiner rejects claims 1-5, 7-13 and 19 under 35 U.S.C. §102(b) as being anticipated by Polivka I (CS 263993) or Polivka II (Coll. Czech. Chem. Commun. 1989, 54(9), 2443-69) The Examiner states that the administration of a pure enantiomer of ketotifen to an animal in need thereof would inherently lead to the corresponding norketotifen, 10-hydroxy ketotifen and 10-hydroxy-norketotifen, which are metabolites of ketotifen. The Examiner considers the lack of side effects of the enantiomer intrinsic to the compound.

By the accompanying amendment, claim 1 has been amended by limiting A to a keto-group and R to hydrogen. Both Polivka I and Polivka II require that R be methyl.

The Examiner rejects claims 1-20 under 35 U.S.C. §103(a) as being unpatentable over Polivka I or Polivka II in view of Le Bigot and Bourquin and Kofler. The Examiner admits that Polivka I and II do not specifically disclose the enantiomers of norketotifen, hydroxy ketotifen and hydroxy-norketotifen, the Examiner states that administration of a pure enantiomer of ketotifen to an animal would lead to the corresponding compound, since they are known metabolites as shown by Bigot. The Examiner also considers that the lack of side effects of the enantiomer is intrinsic to the compound.

By the accompanying amendment, claim 1 has been limited to the stereochemically isomeric forms of norketotifen. In addition, the method claims have been amended to methods of preventing or treating various diseases by administering racemic norketotifen, the optically active isomers of norketotifen, and S-ketotifen, while avoiding the dose-limiting sedative side effects of racemic

ketotifen.

Submitted herewith is a Declaration by Dr. Gunnar Aberg, one of the inventors of the present invention. In the Aberg Declaration, the studies performed by Polivka et al. on the enantiomers of ketotifen are outlined and summarized. In four of the five studies performed, Polivka et al. found that the R-isomer of ketotifen was more active than the S-isomer. Polivka et al. thus teach away from administering S-ketotifen. In addition, nowhere do Polivka et al. disclose or suggest that racemic norketotifen, optical isomers of norketotifen, or S-ketotifen has significantly less sedation than racemic ketotifen as recited in the pertinent claims as amended.

With regard to claim 1 as amended, Applicants wish to point out that the isomerism of ketotifen is of a very unusual type, as no optically active carbon atoms exist in the molecule. The reason for the ketotifen isomerism (called atropisomerism) is not obvious or clear to those skilled in the art. Indeed, the inventors are unaware of any prior art research regarding the importance of the methyl group of ketotifen for its isomerism. It was considered possible that the methyl group may be necessary for the chiral stability of the atropisomers of ketotifen. Accordingly, one skilled in the art cannot conclude that corresponding molecules that are devoid of the N-methyl substituent (e.g., norketotifen) will be resistant to instant racemization. It follows that the skilled artisan has no reasonable expectation that the administration of S-ketotifen will result in the metabolic formation of S-norketotifen. It is far from obvious that an optically active drug has metabolites that are of the same stereochemical configuration since the most common type of biological racemization occurs during the metabolism in the liver (metabolic racemization).

The present inventors have determined that optically active and stable enantiomers of norketotifen actually exist, and have designed synthetic methods for such isomers. Furthermore, as set forth in detail in the accompanying Aberg Declaration, the present inventors have surprisingly

found that isomers of norketotifen reduce or eliminate the sedative side effects of ketotifen. This is nowhere disclosed or suggested by the cited references.

The Examiner states that since Polivka I and II have shown that the R- and S-isomers have different affinities for histamine H-1 receptors, muscarinic receptors and have difference antianaphylactic effect, one of ordinary skill in the art would be motivated to resolve the racemate into pure enantiomers to optimize desired activity.

Applicants respectfully disagree. The biological test results of Polivka teach away from using the claimed S-isomer of ketotifen (see the Aberg Declaration). In general, chemically and metabolically stable eutomers have biological activities that are different from their corresponding distomers, but considering the vast amount of racemic drugs available, only very few optically active isomers have been found that offer important therapeutic advantages over the corresponding racemates.

Reconsideration and allowance are respectfully requested in view of the foregoing.

Respectfully submitted,

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Version with Markings to Show Changes Made

In the specification:

Page 1, after the title, insert:

This application is a §371 of PCT/US00/24892 filed September 12, 2000.

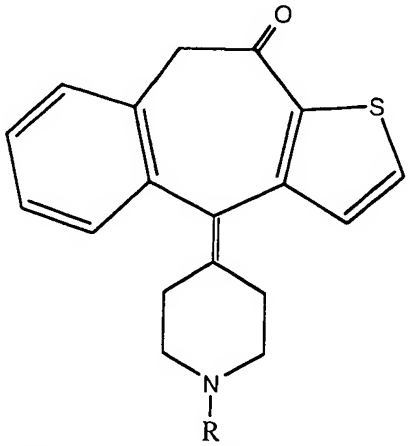
Page 25:

ABSTRACT

Racemic norketotifen, racemic 10-hydroxy-ketotifen, racemic 10-hydroxy-nor-ketotifen and optically active isomers of ketotifen, norketotifen, 10-hydroxy-ketotifen and 10-hydroxy-norketotifen were found to have antiallergic and anti-inflammatory effects while being devoid of the severe dose-limiting sedative side effects of ketotifen.

In the claims:

1. (Amended) [A] The stereochemically isomeric forms of a compound of the structure:



where [A is -CO- or -CHOH- and] R is [CH_3 or] H, [and the stereochemically isomeric forms and diastereomers thereof, with the provisos that

A is not -CO- when R is CH_3,

A is not -CO- when R is H if the compound is a racemate,

A is not -CHOH- when R is CH_3 if the compound is a racemate,

A is not -CHOH- when R is H if the compound is a racemate,] and pharmaceutically acceptable salts and solvates thereof.

2. (Amended) A compound according to claim 1, where [R is H and A is -CO- and] the compound is of the R-configuration.

3. (Amended) A compound according to claim 1, where [R is H and A is -CO- and] the compound is of the S-configuration.

4. (cancelled)

5. (cancelled)

6. (Amended) A method for synthesis of the stereochemically active compounds according to claim 1, [where R is H and A is -CO- and] being of the R- or S-configuration, comprising the conversion of the corresponding stereochemical isomers of ketotifen into their 1-(2,2,2,-trichloro ethoxycarbonyl) nor-intermediates, followed by Cd/Pb-catalyzed cleavage to the products.

7. (Amended) A method for preventing or treating a disease selected from the group consisting of respiratory disorders, allergic disorders, dermal disorders, gastrointestinal disorders and ocular disorders, which comprises administering to a mammal in need [of such treatment] thereof a therapeutically effective amount of a compound selected from the group consisting of racemic norketotifen and stereochemical isomers thereof, the S-isomer [stereochemical isomers] of ketotifen, [racemic 10-hydroxy-ketotifen and the R,R- R,S-, S,R- and S,S-isomers thereof and racemic 10-hydroxy-norketotifen and the R,R-, R,S-, S,R- and S,S-isomers thereof,] or pharmaceutically acceptable salts or solvates thereof, while avoiding the dose-limiting sedative side effects of ketotifen.

16. (cancelled)

17. (cancelled)

20. (Amended) A method of administering to a mammal in need thereof a composition, said composition comprising a therapeutically active amount of racemic or an optically active isomer of norketotifen, [racemic 10-hydroxy-ketotifen, racemic 10-hydroxy-norketotifen] or the S-isomer [an optically active isomer] of ketotifen [or a compound of Claim 1], or a pharmaceutically acceptable salt or solvate thereof together with one or more drugs of the class consisting of adrenergic antagonists, analgesics, antihypertensive agents, calcium antagonists, antihistamines, anticholinergic agents, antibacterial agents, antiviral agents, antiinflammatory agents, bronchodilators, decongestants, steroids, leucotriene antagonists, lipoxygenase inhibitors, local anesthetics, vasoconstrictors, vasodilators, cough suppressants, and expectorants.